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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,777	01/17/2006	Arik Hasson	24024-510 NATL	3627

30623 7590 07/09/2008

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
07/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,777	HASSON ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-15,17-22 and 24-50* is/are pending in the application.

4a) Of the above claim(s) *12,13,15,17 and 24-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,14 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of December 20, 2007, to the non-final action dated August 20, 2007, and the supplemental amendment filed April 4, 2008 have been entered. Claims 1-8, 11-15, 17-22 and 24-50 are pending in the application. Claims 9, 10, 16 and 23 have been cancelled and claims 1, 2 and 11 amended. No claims were newly added. Claims 12, 13, 15, 17 and 24-50 stand withdrawn from further consideration, with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 1-8, 11, 14 and 18-22 are currently under examination.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1-11, 14, 16 and 18-23 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants' cancellation of claims 9, 10, 16 and 23 renders their rejections moot. The rejection set forth on pp. 3-4 of the previous office action dated August 20, 2007 is maintained for claims 1-8, 11, 14 and 18-22 reasons of record.

Applicants argue that claim 1 has been amended to recite "A method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time, inhibiting differentiation of the stem and/or progenitor cells…", thereby overcoming the rejection.

Such is not found persuasive, because amended claim 1 continues to recite "while at the same time, substantially inhibiting differentiation"; contrary to Applicants' assertion. Applicants should further note that claim 1 does not recite "hematopoietic stem and/or progenitor cells", but is broadly directed to "stem and/or progenitor cells", although claim examination has been limited to the elected species of hematopoietic stem cells.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-11, 14, 16 and 18-23 stand rejected in modified form under 35 U.S.C.§112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants' cancellation of claims 9, 10, 16 and 23 renders their rejections moot. The rejection set forth on pp. 4-7 of the previous office action dated August 20, 2007 is maintained for claims 1-8, 11, 14 and 18-22 reasons of record.

The previous office action indicated an enabled scope for a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising culturing $CD34^+$ and/or $CD133^+$ enriched undifferentiated hematopoietic stem and/or progenitor cells derived from bone marrow, mobilized peripheral blood or umbilical cord blood, in a bioreactor under conditions comprising the cytokines TPO, IL-6, SCF, and FLT-3 ligand, and 2-15 μM of copper chelator tetraethylenepentamine.

Applicants' amendment of base claim 1 to recite that the copper chelator is tetraethylenepentamine (TEPA), only in part obviates the grounds for rejection. It was indicated that the disclosure is not enabled for *ex-vivo* culture and expansion and inhibition of differentiation of hematopoietic stem/progenitor cells that did not undergo pre-selection and enrichment for CD34+ or CD133+ stem cell markers.

Applicants disagree, arguing Example 2 of the instant specification shows enhanced expansion of hematopoietic stem and/or progenitor cells (HSC) from unselected, total nucleated cells from the leukocyte-rich fraction of blood using the methods of the claimed invention, as evidenced by fold expansion of the total cellular, CD34+ and CD133+ fractions. Applicants' arguments have been fully considered, but are not found persuasive.

It should be noted that Example II, builds on the teachings of Example I, wherein it is taught that mononuclear cells were collected from either bone marrow, mobilized peripheral blood or umbilical cord blood and hematopoietic stem/progenitor cells are isolated by magnetic activated cell sorting, prior to being seeded for culture (lines 13-17, p. 97). Example II extends the teachings in Example I, by assessing the efficacy of different bioreactor conditions on expansion

of HSC cultures (lines 8-12, p. 98). The fact that total nucleated cells may be culture expanded is not the issue. The issue is that the HSCs are taught as a sub-population of magnetically sorted CD34+ and CD133+ cells, and not any type of hematopoietic stem cell. Examples 1 and 2 describe the culture of mononuclear $CD34^+$ and mesenchymal $CD133^+$ stem cells respectively, isolated by magnetic activated cell sorting, and their subsequent culture in the presence of 10% FCS, and 50 ng/ml of cytokines TPO, IL-6, SCF, and FLT-3 ligand. Additionally teaching that the inclusion of 5μM of copper chelator tetraethylenepentamine (TEPA) dramatically increased the expansion of the immature subpopulation of hematopoietic stem and/or progenitor cells.

As a separate issue, the office action indicated that the instant claims embrace a method of *ex-vivo* expanding hematopoietic stem and/or progenitor cells, while at the same time inhibiting the differentiation of the stem and/or progenitor cells comprising obtaining any population of hematopoietic cells comprising stem and/or progenitor cells and culturing the mixed population of cells in a bioreactor comprising a copper chelator at any concentration, in an undefined medium. However, the specification is devoid of any teaching for culturing and expanding stem cells in the presence any concentration of any copper chelator, or in the absence of specific cytokine combinations.

Applicants disagree that the art of growing undifferentiated stem cell in culture is unpredictable and that, even for the same stem cell type, various culture conditions do not render the same results, arguing that Peters et al. reported on experiments using fetal liver (FL) putative hematopoietic cells. The cited passage relates to expansion of total FL cell numbers (see Peters et al., Fig. 1) over 60 days of culture, and does not provide any assessment of the stage of differentiation of the expanded. Further determinations of CD34+ expansion were conducted in "CI" expanded cultures, without comparison of culture conditions.

Such is not found persuasive, because the teachings of Peters et al. are directed to "long-term *ex-vivo* expansion of human fetal liver primitive haematopoietic progenitor cells in stroma-free cultures" (Title), The authors state: "We tested a large series of culture conditions, including those used successfully with CB CD34+ cells, but only one of them sustained long-term, massive expansion of FL hematopoietic cells, reaching over 3 x 10^7-fold input cell number after 150 days in culture". Further stating that defining optimal culture parameters for *ex vivo* expansion has

been a challenge, and that the FL represents a promising alternative source for HSC (Abstract). The prior art of Peters et al. has been cited as an example of the prior art's teaching regarding the difficulty and unpredictability in determining optimal long-term culture conditions for stem cells. To that end, the cited art is pertinent to the instant rejection.

Applicants argue that Percival et al. studied the effects of copper on retinoic acid stimulated differentiation (superoxide anion production) of a single *in-vitro* cell line, HL-60, which lacks the capability for spontaneous differentiation. Thus, Percival et al. did not study *ex-vivo* expansion and differentiation of hematopoietic cells as taught in the instant specification.

Such is not found persuasive, because Percival et al. has not been cited to anticipate the instant claims, but rather to indicate the determination for the role of copper chelator TEPA in differentiation requires further research. Percival et al. showed that cells incubated with TEPA and retinoic acid produced the same amount of superoxide anion as did the cells with retinoic acid, indicating that the cells still underwent differentiation, suggesting more work may be required to understand the role of copper chelator in expansion of HSC (p. 1066S, 2nd column,, 2nd paragraph).

Applicants' arguments regarding chelators EDTA and citrate are moot in view of the claim amendments limiting the copper chelator to TEPA. Applicants argue the feature of the presence of specific combinations and concentrations of cytokines and nutrients, as for example disclosed in Examples 1 and 2, is but one embodiment of the actual invention; further arguing that while a detailed understanding of the mechanisms of expansion proliferation, expansion and differentiation of stem cells will undoubtedly be of great value, such understanding is not necessary for enabling the claimed invention.

Such is not found persuasive, because as indicated on the record, the art of culturing, expanding and preventing the differentiation of hematopoietic stem cells in the presence of TEPA is not considered routine, and the unpredictability in the art is one of the Wands factors to be considered in the determination of an enabling disclosure. An enabled scope has been indicated for the instant claims. The claim rejection does not indicated a total lack of enablement for the broadly claimed invention. The issue is whether a person of skill in the art would be able

to reasonably carry out the instantly claimed method using any concentration of TEPA and any "early cytokine" combination without further undue experimentation. As previously indicated by Lovejoy et al. (Blood 100:666-676; 2002), iron chelators , even at concentrations below 0.5 μM can significantly inhibit growth of normal bone marrow stem cells. Therefore, a person of skill in the art would have to engage in additional experimentation to determine whether any concentration of copper chelator may be used to expand hematopoietic stem cells while inhibiting their differentiation.

With respect to Applicants' citation of PCT IL/99/00444 (WO 2000/018885), incorporated by reference, it is noted that the Application fails to show culturing in the presence of any early acting cytokine, but appears to recite only those early cytokines described in the instant specification. The prior art has repeatedly demonstrated that with regard to the differentiation of stem cells, culture conditions comprising the inclusion or omission of certain cytokine combinations can either promote or inhibit differentiation, and the instant specification only demonstrate conditions inclusive of TPO, IL-6, SCF, and FLT-3 ligand, and 2-15 μM of copper chelator TEPA.

Thus, the rejection of claims 1-11, 14, 16 and 18-23 is maintained for reasons of record and the foregoing commentary.

Response to Claim Rejections - 35 USC § 102

Claims 1-11, 14, 18 and 23 were rejected under 35 U.S.C. 102(b) as being anticipated by PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in the office action dated August 20, 2007. Applicants' cancellation of claims 9, 10 and 23 renders their rejections moot. In view of Applicants' amendment of base claim 1, introducing the limitation "stirred flask or rotating wall vessel", as the bioreactor, that is not taught by Peled et al., the previous rejection is rendered moot and hereby withdrawn. The claims are however subject to new rejections over the prior art of record, as set forth below.

Response & New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1, and 6 were rejected under 35 U.S.C. §103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Lipton et al. (U.S. Patent Publication No: 2002/0090603; effective filing date June 5, 2001); claims 1 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Wager et al. (U.S. Patent Publication No.: 2002/0001826; filed Dec. 21, 2000); and claims 1 and 19-22 were rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Itskovitz-Eldor et al. (U.S. Patent No.: 7,247,477; filed Aug. 5, 2002),), in the office action dated August 20, 2007. Applicants' cancellation of claim 16 renders its rejections moot.

In view of Applicants' amendment of base claim 1, introducing the limitation "stirred flask or rotating wall vessel", as the bioreactor, the previous rejections of claims 6, and 19-22 are hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. The claims are however subject to new rejections over the prior art of record, as set forth below.

The rejection over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Wager et al. (U.S. Patent Publication No.: 2002/0001826; filed Dec. 21, 2000), set forth on pp. 9-10 of the previous office action dated August 20, 2007 is maintained for claim 1 and newly applied to claims 2-5, 7, 8, 11, 14 and 18 for reasons of record.

To the extent that Applicants' arguments are pertinent to the standing rejection of claim 1, and the new rejections, they are addressed as follows:

Applicants disagree with the rejection of claim 1 over Peled in view of Wagner, arguing that Wagner teaches away form the method of the claimed invention, because hematopoietic cells grown according to the methods of Wager et al. invariably differentiate into mature blood cell types, and no means for inhibiting differentiation is provided; that Wager et al. emphasize

and demonstrate the cellular differentiating capabilities of their stromal cell lines, and the confluent stromal cell layer described by Wager et al is incompatible with the methods of expanding and inhibiting differentiation of stem and/or progenitor cells as claimed in the present invention. Applicants' arguments have been fully considered, but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of Wagner et al. to formulate the grounds for teaching away. It should be noted that the ultimate goal of expanding hematopoietic stem cells is to provide for their ultimate differentiation. As previously indicated, Wager et al. in describing a method for the culture of hematopoietic stem cells (Abstract), state: "precursor cells may be cultured in any vessel which is capable of being sterilized, is adapted or adaptable to gas exchange with the atmosphere, and is constructed of a material which is non-toxic to cells. A variety of vessels suitable for this purpose are well-known in the art, including stirring flasks (Coming, Inc., Coming, N.Y.), stirred tank reactors (Verax, Lebanon, N.H.)" etc. (paragraph [0050], p. 12). Thus, Wager et al. cure the deficiency in Peled et al. for culture of hematopoietic stem or progenitor cells in stirring flasks. To the extent that Wagner et al. describe the culture of hematopoietic stem cells in stirring flasks, the rejection is applicable to the instant case. Applicants' selective reading of Peled et al. ignores the teachings of the primary reference of Peled et al. There is no requirement for Peled et al. to teach that which is clearly taught by Peled et al. A person of skill in the art would be motivated to culture hematopoietic stem cells in stirred flasks, because the method would allow for scale up for the production of hematopoeitic stem or progenitor cells in large numbers, with a reasonable expectation of success.

Applicants further argue unexpected superior expansion of hematopoietic cells, because the fold expansion of CD133+ and CD133+/CD34- cells (early hematopoietic progenitors) grown in stirred flask or rotating wall vessel bioreactors was consistently greater by 10 to 40% or more than the static-grown cultures, considering the previous methods for growing stem and/or progenitor cells in bioreactors required the a stromal cell or feeder layer.

Such is not found persuasive because any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Peled et al. teach that long-term culture of $CD34^+$ cell cultures in the presence of TEPA, may be carried out in the absence of stroma or a feeder layer, thus the relevance of Applicants' arguments with respect to attachment of stromal cells is not apparent. Further, the expansion of hematopoietic cells in stirring flasks and stirred tank reactors including stirring and shaking are described by Wagner et al. Such methodology for scale up and expansion of cultured cells was considered routine in the prior art. Therefore the fact that hematopoietic cells may be expanded to a greater extent in stirred flasks than in static culture bags is an expected result, and is the goal behind scale up culture. As indicated in MPEP 716.02(c), Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1 and 6 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Wager et al. (U.S. Patent Publication No.: 2002/0001826; filed Dec. 21, 2000), as applied to claims 1-5, 7, 8, 11, 14 and 18, above, and further in view of in view of Lipton et al. (U.S. Patent Publication No: 2002/0090603; effective filing date June 5, 2001).

Peled et al. describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, p. 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20). Wager et al. in

describing a method for the culture of hematopoietic stem cells (Abstract), state: "precursor cells may be cultured in any vessel which is capable of being sterilized, is adapted or adaptable to gas exchange with the atmosphere, and is constructed of a material which is non-toxic to cells. A variety of vessels suitable for this purpose are well-known in the art, including stirring flasks (Coming, Inc., Coming, N.Y.), stirred tank reactors (Verax, Lebanon, N.H.)" etc. (paragraph [0050], p. 12). Thus, Wager et al. cure the deficiency in Peled et al. for culture of hematopoietic stem or progenitor cells in stirring flasks.

While Peled et al. describe the selection of hematopoietic stem cells via CD34, neither Peled et al. nor Wagner et al. describe affecting the selection via CD133. However, Lipton et al. in describing methods of differentiating progenitor state: "Methods of preparing progenitor or stem cell populations enriched for particular markers are well known in the art. For example, a CD133-positive/CD34-positive hematopoietic stem and progenitor cells can be prepared as set forth in Yin et al., Blood 90:5002-5012 (1997)" (paragraph [0108]). Thus, Lipton et al. cure the deficiency in Peled et al. and Wagner et al. for selecting a population of hematopoietic stem cells enriched for $CD133^{+}$ progenitor cells.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Peled et al., Wagner et al. and Lipton et al. to enrich hematopoietic stem cells using $CD34^{+}$ and/or $CD133^{+}$ cell surface markers, and *ex vivo* expand hematopoietic stem cells in stirred flasks as a matter of design choice, in the method of culturing and expanding hematopoietic stem or progenitor cells, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. Said design choice amounting to combining prior art elements according to known methods to yield predictable results.

It should be noted that the *KSR* case forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http: www. Uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Claims 1 and 19-22 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over PCT Publication WO 99/40783 (inventors: Peled et al.; Published 19 August 1999), in view of Wager et al. (U.S. Patent Publication No.: 2002/0001826; filed Dec. 21, 2000), as applied to claims 1-5, 7, 8, 11, 14 and 18, above, and further in view of Itskovitz-Eldor et al. (U.S. Patent No.: 7,247,477; filed Aug. 5, 2002).

Peled et al. describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, p. 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20). Wager et al. in describing a method for the culture of hematopoietic stem cells (Abstract), state: "precursor cells may be cultured in any vessel which is capable of being sterilized, is adapted or adaptable to gas exchange with the atmosphere, and is constructed of a material which is non-toxic to cells. A variety of vessels suitable for this purpose are well-known in the art, including stirring flasks (Coming, Inc., Coming, N.Y.), stirred tank reactors (Verax, Lebanon, N.H.)" etc. (paragraph [0050], p. 12). Thus, Wager et al. cure the deficiency in Peled et al. for culture of hematopoietic stem or progenitor cells in stirring flasks.

While Peled et al. describe the culture of hematopoietic stem cells in culture dishes , and Wagner et al describe culturing precursor cells in stirring flasks, they do not describe cell culture on a porous scaffold comprising alginate or a hydrogel. However, Itskovitz-Eldor et al. in describing methods for the culture vasculogenic progenitor cells from stem cells (lines 14-16, column 1), state that according to preferred embodiments of their invention, the population of progenitor cells is cultured in semi-solid medium of on a 3-dimentional scaffold (limitation of claim 19). The seeding of the progenitor cells on 3-D alginate scaffolds is depicted in Figs. 4A-B, further showing vascularization in scaffold pores (limitations of claims 20 and 22); additionally teaching that the substrate may be a matrigel or collagen gel (lines 14-15. column 7; Fig. 3B), that constitute different hydrogels (limitation of claim 21). Thus, Itskovitz-Eldor et al. cure the deficiency in Peled et al. and Wagner et al. for culture of hematopoietic stem or progenitor cells on porous scaffold comprising alginate or a hydrogel.

By describing the *in vitro* culture and differentiation of their progenitor cells in 3-D alginate scaffolds (Figs. 4A an 4B), Itskovitz-Eldor et al. provide the motivation to one of ordinary skill in the art to adopt the methodology to appropriate stem cells of interest.

Therefore, a person of ordinary skill in the art would have been motivated to combine the respective teachings of Peled et al. Wagner et al. and Itskovitz-Eldor et al. to culture and differentiate hematopoietic stem cells on 3-D alginate porous scaffolds, in stirring flasks as instantly claimed, with a reasonable expectation of success, because the differentiation of the stem/progenitor cells may be achieved by alterations in medium composition.

Thus it would have been *prima facie* obvious for a person of ordinary skill in the art, to effect culture of hematopoietic stem or progenitor cells on 3-D alginate porous scaffolds in stirring flasks, at the time of the instant invention.

Response to Obviousness Type Double Patenting

Claims 1, 2-5, 7-11, 14 and 23 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 8-11 of U.S. Patent No. 7,169,605; claims 1, 2-5, 7-11, and 23 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, and 8-15, 121, 123, 124, 126-128 and 131 of copending U.S. Patent Application No.: 10,418,639; and claims 1, 2-11, and 23 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 201, 209, and 212, 213 and 238 of copending U.S. Patent Application No.: 10,767,064; in the office action dated August 20, 2007. Applicants' cancellation of claims 9, 10 and 23 renders their rejections moot. In view of Applicants' terminal disclaimer dated December 20, 2007, the previous rejections are rendered moot and hereby withdrawn.

Conclusion

Claims 1-8, 11, 14 and 18-22 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633